Prostate cancer detection in men with an initial diagnosis of atypical small acinar proliferation

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OBJECTIVE
To determine the subsequent prostatic adenocarcinoma detection rate amongst men with an initial diagnosis of atypical small acinar proliferation (ASAP).

PATIENTS AND METHODS
We reviewed the Illawarra Prostate Pathology Database over a 10-year period (January 1994 to January 2004) for specimens diagnosed as ASAP. These specimens were re-reviewed and clinical data obtained.

RESULTS
Of 61 cases of ASAP, there were complete follow-up data for 31. In this group nine patients had no further biopsies at our institution; the other 22 had at least one repeat biopsy. The incidence of prostatic adenocarcinoma in this group was 17/31 (55%). This included 13 diagnoses on second biopsy, three on third biopsy and one diagnosed at another institution.

CONCLUSION
This study showed a detection rate for prostatic adenocarcinoma of 55% after an initial diagnosis of ASAP, which indicates that an initial diagnosis of ASAP mandates re-biopsy.

KEYWORDS
atypical small acinar proliferations; prostate neoplasms; premalignant

INTRODUCTION
Although diagnosing ‘atypical glands suspicious for carcinoma’ on a prostate biopsy is not new, nor attributable to a specific author, the term ‘atypical small acinar proliferation (ASAP)’ was first coined by Bostwick et al. in 1993 [1], who described ASAP as denoting the presence of suspicious glands with insufficient cytological or architectural atypia for a definitive cancer diagnosis. Whilst there are no features specific to ASAP, the following histological differences in combination are often seen when compared with adenocarcinoma: smaller foci (mean of 0.4 mm in ASAP vs 0.8 mm in minimal cancer), fewer acini involved (mean of 11 in ASAP vs 17 in minimal cancer), lack of infiltrating growth, absence of mitotic figures, prominent nucleoli in <10% of cells, lower incidence of nuclear enlargement, lower incidence of hyperchromasia, and lack of blue mucin secretions [2].

Essentially a pathological term indicative of diagnostic uncertainty, the incidence of ASAP in prostatic biopsies is 1.5–9% in unselected series [3–7]. The clinical importance of ASAP is its high predictive value for prostatic adenocarcinoma in subsequent biopsies. The predictive values obtained for cancer on a second biopsy are 34–70% in similar studies [4,8–12]. This incidence is generally accepted to be higher than biopsies solely based on clinical suspicion [12,13] or after an initial biopsy diagnosis of the premalignant condition high-grade intraepithelial neoplasia (HGPIN) [12,14–16].

PATIENTS AND METHODS
The Illawarra Prostate Pathology Database was reviewed for diagnoses of ASAP for the 10-year period January 1994 to January 2004. Of 1632 specimens reviewed, those with a diagnosis of ASAP were re-reviewed by two independent histopathologists. Where they concurred on the diagnosis of ASAP, clinical and follow-up data were obtained.

Exclusion criteria were: a concomitant diagnosis of prostatic adenocarcinoma (i.e. fulfilling the diagnostic threshold), exclusion of additional ASAP specimens in a patient already in the cohort, or a previous history of prostatic adenocarcinoma. This produced a study cohort of 31 patients from 64 ASAP-positive specimens in the prostate database, representing 1.9% of the 1632 specimens reviewed. This compares with 101 patients in the same database being diagnosed with HGPIN (6.2% of specimens). In all 31 patients, the following fields were recorded retrospectively: age, initial DRE result, initial PSA level, initial result of immunohistochemical labelling for cytokeratin 34BE12, number and outcome of subsequent biopsies, interval in months between biopsies, and Gleason score where relevant.

RESULTS
The 31 patients had a median (range) age of 65 (53–78) years, a PSA level of 7.6 (0.3–36) ng/mL and a DRE reported as normal in 28/31 (90%). Two men (6.5%) had a concomitant diagnosis of HGPIN made on initial biopsy. Of the 31 men, nine (29%) had no repeat biopsy, in all cases this was due to patient preference. Of these nine, one had a TURP with the pathology returning as benign; the other eight were regularly followed-up with repeat PSA tests. The mean follow-up was 51.4 (1–97) months. In this group, one man was found to have adenocarcinoma of the prostate. It was established that, after his
initial diagnosis of ASAP, he presented for investigation to another institution, with haematuria. At that time he elected to have a repeat biopsy, which showed prostatic adenocarcinoma, and he was treated with external beam radiotherapy. There were no other diagnoses of prostatic adenocarcinoma in this group.

The other 22 men (79%) had a second biopsy at a median of 8 (2-36) months after the first. The results of the second biopsy were: prostatic adenocarcinoma in 13 men (59%), ASAP in five (23%), and benign pathology in four (18%). Of the 13 prostatic adenocarcinomas, the median Gleason score was 3 + 4 = 7 (range 6-9), including six that were 2+3 = 5. Eight of these patients were managed by radical prostatectomy (RP), four by brachytherapy (supplemented with androgen deprivation therapy in one patient with a Gleason score of 4 + 5 = 9), and one by watchful waiting.

Five men with an initial biopsy result of ASAP also had a diagnosis of ASAP on second biopsy. In all five cases a third biopsy was performed, at a median of 14 (12–60) months after the second. In all five cases a third biopsy was also had a diagnosis of ASAP on second biopsy, both of the men who were diagnosed with prostatic adenocarcinoma after two ASAP results had 20 cores taken. The one man who was diagnosed with prostatic adenocarcinoma after a benign second biopsy result had 10 cores taken.

The results of the third biopsy were: ASAP (one), benign pathology (two) and prostatic adenocarcinoma (two). The two cancers were 4 + 3 = 7 and 3 + 3 = 6, and both were treated with RP.

Four men with an initial biopsy result of ASAP had a second biopsy showing benign pathology. All four had a third biopsy at a median of 19.3 (12–36) months after the second. The results of the third biopsies were ASAP in one patient, benign pathology in two, and prostatic adenocarcinoma in one. The carcinoma was 4 + 3 = 7, it was managed by RP.

At our institution, an initial biopsy typically involves taking 10 cores, sampled bilaterally from the base, upper mid, lower mid, mid, and apical aspects of the lobes. Of the 31 patients, 28 had an initial biopsy, i.e. the biopsy showing ASAP, which involved 10 cores. Two men had an initial biopsy with six cores, and one had an initial biopsy with 20 cores; no explanation was documented for the altered approach in these three men.

Of 22 men who had a second biopsy, 12 (55%) had 20 cores and 10 (46%) had 10 cores taken. In those with 20 cores, 10 cores were as per the 10-core biopsy protocol, and 10 were from bilateral sampling of the anterior zone (upper and lower) and the transitional zone (upper, middle and lower).

Of the 13 men diagnosed with prostatic adenocarcinoma on second biopsy, six had 10 cores and seven had 20 cores taken. On third biopsy, both of the men who were diagnosed with prostatic adenocarcinoma after two ASAP results had 20 cores taken. The one man who was diagnosed with prostatic adenocarcinoma after a benign second biopsy result had 10 cores taken.

Overall, of 31 patients, 17 had a subsequent diagnosis of prostatic adenocarcinoma; Table 1 shows the Gleason scores and when the diagnosis was made. This gave a subsequent detection rate of 55% after an initial biopsy result of ASAP. The median (range) Gleason score was 3 + 4 = 7 (6–9) and eight patients had a Gleason score of ≥ 4 + 3 = 7.

**DISCUSSION**

There has been increasing use of thin-core biopsies of the prostate for investigating men with clinical or biochemical evidence of prostatic adenocarcinoma. In a few of these biopsies, no definitive diagnosis is possible due to the limited size and architecture of the specimen. Accordingly, the term ASAP has entered the pathological vernacular to indicate diagnostic uncertainty [17]. Unlike the premalignant condition of HGPIN, ASAP is not a single entity, but encompasses a diverse array of lesions such as basal cell hyperplasia, adenosis, benign crowded glands and reactive atypia [18]. It might also represent a focus of cancer that, because of how it is sampled, does not attain the diagnostic threshold for carcinoma [19] (Fig 1).

Despite the general acceptance of ASAP as a pathological entity, there have been criticisms. These include the notion that ASAP legitimises pathological uncertainty by expressing it in terms that appear to be a diagnosis [20]. A second concern is that several large series showed a re-biopsy rate of <70% after a diagnosis of ASAP [8,9,19,21,22], raising concern that the term ASAP does not adequately convey the seriousness of the biopsy result to either the urologist or patient [18]. A third problem with ASAP is the presence of high interobserver variability. Concordance rates of 84% and 78% between independent pathologists were described in two large studies [10,23]. Thus the 'diagnosis' of ASAP might be subject to debate. In addition, there are difficulties in interpreting the ASAP foci, which include the small size of the focus, disappearance on step levels, and...
lack of significant cytological abnormalities, raising the possibility of one of many mimics of adenocarcinoma [8].

Despite these shortcomings, it is clear from the present retrospective review that an initial diagnosis of ASAP conveys a greater risk of prostatic adenocarcinoma on repeat biopsy. Of 31 patients initially diagnosed with ASAP on biopsy, 22 had at least one repeat biopsy, and 16 of these (73%) were found to have prostatic adenocarcinoma. This rate is a higher positive re-biopsy rate than in 11 similar studies. The positive re-biopsy rates in 12 other studies were 36–100% (median 47%) [4,8,10–13,15,19,22–25].

A possible reason for the relatively high rate of prostatic adenocarcinoma in the present study, after an initial diagnosis of ASAP, is our biopsy regimen; 90% of the 31 patients had 10 cores taken at the time of their diagnosis of ASAP. This is more extensive sampling than the usual sextant biopsy technique used by many centres. On second biopsy, 12 of 22 patients had 20 cores taken and the other 10 had 10 cores, compared with six [20], 8–10 [13], 11 [12] and 10–12 [11] cores on second biopsy in studies with lower detection rates of prostatic adenocarcinoma after an initial ASAP diagnosis. Indeed, the only series with a higher rate of prostate cancer after an initial diagnosis of ASAP was at a unit that performed RP on all patients. By taking more cores, we might have been able to provide sufficient histological and cytological samples to allow for a definitive diagnosis of prostatic adenocarcinoma, where fewer samples might not have allowed for this.

In addition to a high positive re-biopsy rate, the present cases tended to have relatively high-grade cancer, as determined by Gleason score, than had other studies. In the present study, 14 of 17 (82%) cancers were diagnosed with a Gleason score of ≥7, compared with 16% [23], 22% [19], 36% [11], and 39% [24] in four other large studies. This finding of proportionately more high-grade cancers is despite the present cohort having a median time to second biopsy of 8 months, which did not differ significantly from similar studies [1,11,24]. In addition, the time between initial and repeat biopsies was not a statistically significant predictor of a positive second biopsy result in these studies.

The high positive repeat biopsy rate in the present cohort implies that all men with an initial diagnosis of ASAP require at least a second biopsy. This opinion concurs with that proposed by other studies with lower positive re-biopsy rates [26].

The timing of repeat biopsy has yet to be determined, with no studies showing an optimum time for cancer detection. However, it was advocated that a second biopsy should be at 3 months, as there is no particular reason for delaying re-biopsy in an individual at high risk for malignancy [27]. While delaying a second biopsy is not advantageous, logistical factors, patient preference and the slowly progressing nature of prostatic adenocarcinoma might require that the interval between the first and second biopsies to be >3 months.

Another issue to be considered when re-biopsying the patient is the biopsy site. Could the re-biopsy be localized to the initial focus of ASAP, or is more extensive sampling necessary? In articles reviewed, the positive cores on re-biopsy were contralateral to the original ASAP focus in up to 39% of cases. This implies that limiting the second biopsy to the involved sextant site or even the ipsilateral side would produce a significant number of false-negative results. Therefore, it is recommended that repeat biopsy should include bilateral biopsies of the standard sextant locations [21,28]. However, it seems prudent to take multiple samples of the atypical area found on initial biopsy.

In the present cohort, the cancer detection rate on third biopsy was three of nine patients. These included five men with ASAP and four with benign pathology on second biopsy. This compared to positive rates on third biopsy of 16% [11] and 33% [29] in two similar studies. A possible explanation for this relatively high positive third biopsy rate is the extensive sampling used at our institution; these men had 30–50 cores taken over the course of the three biopsies.

The implication of this high rate of cancer on third biopsy is that, even if a second biopsy is negative for cancer, a man with an initial diagnosis of ASAP should have a third biopsy. This is especially important if the man had two biopsies that only sampled in the sextant locations, as this would only represent 12 cores. However, as only ~60% of patients consent to a second biopsy, it might be difficult to implement mandatory third biopsies after two results negative for cancer.

At the very least, a man with a diagnosis of ASAP and negative re-biopsy needs close monitoring with serial PSA measurements and DREs, and a third biopsy if these or other clinical variables indicate it.

Whilst re-biopsying all men with an initial diagnosis of ASAP is now considered mandatory, a subsequent cancer detection rate of ~50% led one unit to consider more aggressive management of these patients. Brausi et al. [23] performed RPs on 25 men with a diagnosis of ASAP; all 25 had a final pathological diagnosis of adenocarcinoma. However, these men had relatively low-grade tumours; only four (16%) had tumours with a Gleason score of ≥7. This contrasts to the present study, where 73% of patients were shown to have cancer on repeat biopsies, and 82% had a Gleason score of ≥7. This could indicate that ASAP represents ‘a marginally sampled, tangentially sectioned or out-pouching prostatic adenocarcinoma’ [30] and should be treated aggressively. However, as ASAP represents benign mimickers of prostate adenocarcinoma in some cases, prophylactic RP in all men diagnosed with ASAP would undoubtedly lead to men with benign disease being operated on. As RP has associated morbidity and mortality, recommending it for men with no definitive diagnosis of prostatic adenocarcinoma seems unacceptable. Thus, larger studies on the benefits of RP and other aggressive strategies for men diagnosed with ASAP are needed before they become the treatment of choice.

In conclusion, the present cohort of 31 patients with an initial biopsy diagnosis of ASAP, to our knowledge the largest data set published from Australia, had subsequent detection of prostatic adenocarcinoma in 55%, with a median Gleason score of 7. These results, which concur with similar studies, indicate that an initial diagnosis of ASAP mandates re-biopsy.

CONFLICT OF INTEREST
None declared.

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Abbreviations: ASAP, atypical small acinar proliferation; HGPIN, high-grade intraepithelial neoplasia; RP, radical prostatectomy.